USE OF MEPROBAMATE IN TENSION STATES

By

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IN RECENT YEARS a number of new drugs have appeared, grouped together as so-called tranquillizing agents. The publication of three very encouraging papers describing the use of meprobamate prompted the present trial. Selling (1955) prescribed one 400 mg. tablet daily after each meal and one at bedtime in 187 cases, combined with psychotherapy, and found its use in anxiety and tension states was of considerable value (90 per cent and 95 per cent respectively improved or recovered). Borrus (1955) used one to six 400 mg. tablets daily in 104 cases. In 68 per cent of all cases, and 78 per cent of the anxiety states, there were favourable results. Lemere (1955) contrasting chlorpromazine and reserpine, found meprobamate (used in over 250 patients with at least 70 per cent good results) to be relatively uniform in its action, remarkably free from side reaction and more effective in the relief of insomnia. All three authors stressed the absence of toxicity.

Meprobamate is related to mephenesin and other propanediol derivatives, chemically 2-methyl-2-n-propyl-1, 3-propanediol dicarbamate. Berger (1954), describing the pharmacology, reported its use as an interneuronal blocking agent and muscle relaxant without affecting respiration and other vital functions.

METHOD

The present study was made on 41 out-patients, in two separate groups. The first group consisted of 23 patients who received the active drug or a placebo, each made up in identical tablet form, in alternate courses at each visit to the clinic. The therapist remained ignorant of the preparation dispensed, since the key was known only by the chief pharmacist. The average duration of treatment was two months, but in equivocal cases continued over a longer period.

The second group consisted of 18 patients receiving only the active drug. A few were commenced on the active drug before placebo tablets were available, the remainder were cases of long duration who had not responded to previous pharmacological and psychotherapeutic treatment, and upon whom suggestion had had little effect in the past.

The selection of patients was restricted to those showing tension irrespective of diagnosis, and the great majority were suffering from either acute or chronic anxiety states, or depression associated with tension.

The dosage used was 400 mg. three or four times daily as suggested by Selling, apart from five cases where 800 mg. was later prescribed at each dose.

RESULTS

The results are summarized in the accompanying table. "Much improved" is limited to relief of tension, "moderately improved" indicates benefit of some degree with continuation of symptoms, "not improved" includes temporary or slight relief. Patients who felt equally improved on active drug and placebo,

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or improved while taking the placebo and not while taking the active drug, were excluded.

	Much Improved	Moderately Improved	Not Improved	Total
Group I				
Anxiety States	1	1	11	13
Depression associated with tension	1	—	7	8
Obsessive-Compulsive States	—	—	2	2
Group II				
Anxiety States	1	—	6	7
Depression associated with tension	1	2	5	8
Obsessive-Compulsive States	—	—	1	1
Impotence	—	—	2	2
	4	3	34	41

In Group I, two patients were much improved taking the active drug only. One case treated with E.C.T. for a depressive illness was improved, but retained a number of somatic symptoms. Receiving the drug she felt less irritable and more placid, then during a period on placebo felt worse again, but responded once more to the active drug by complaining of less tension and pain and stated she was sleeping better. The second improved case in this group did not respond to the placebo, complained of her head feeling peculiar the first two days on active drug and subsequently felt more relaxed. One moderately improved patient felt steadier on the active drug, felt worse taking the placebo, then receiving the active drug again remarked, "You feel as though you've taken a sedative."

The importance of controlled blind studies has been repeatedly stressed in a number of recent publications. This was borne out by observations in a number of patients. One chronically anxious patient felt "wonderful" the first week of four on placebo. A highly intelligent man, complaining of tension and excessive perspiration, felt calmer during a period later revealed as taking placebo. Another very intelligent patient, a woman suffering with longstanding obsessive-compulsive symptoms, felt improved, less anxious or unhappy during a placebo period. She remarked it was "certainly not faith" as she was very dubious of all new remedies.

In Group II, two patients were improved. A man suffering from headaches due to a mild depressive illness felt brighter and livelier. He left off taking tablets after three months and developed a recurrence of tightness across his head, which was again helped by treatment. The second patient, a chronically anxious woman who suffered with frequent bouts of diarrhoea, became less tense, although after a few weeks she relapsed for a period of three weeks, but then improved again. An interesting effect was produced when at a later date the dosage was increased to 800 mg. t.d.s. She felt calmer after the first dose but *stimulated* after the second dose. This occurred again after first leaving off treatment for a few days. There were two moderately improved cases, one depressed patient slept better although she did not benefit by day, and a second depressed patient felt some sedative effect.

Toxicity and Side-Effects

As mentioned above, the three authors quoted stressed the absence of toxicity. More recent publications, however, have recorded a number of adverse

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reactions. Friedman and Marmelzat (1956) report a number of cases, the reactions including cutaneous, muscular, gastro-intestinal, and paradoxical cerebral effects. They described five cases in which purpuric rashes occurred, three cases of excitement instead of sedation, one case of diarrhoea, and one of extraocular palsy. Lemere (1956) thought the drug habit-forming in some cases, occasionally producing withdrawal symptoms (one patient taking large doses had a convulsion ten hours after discontinuation), and pointed out the need to watch for excessive self-medication in alcoholics. In spite of these drawbacks the author regarded meprobamate as a most useful drug for the relief of tension. Leiberman and Vaughan (1956) reported that many patients were disturbed by muscular weakness and lassitude. An annotation in the *British Medical Journal* (1956) drew attention to the incidence of toxic effects.

In the present series two patients complained of drowsiness (one for only the first few days of treatment), one patient complained that headaches from which she suffered were made worse, two cases of skin disturbance occurred (one patient developed erythema and urticaria lasting 24 hours twice within a few hours of taking one tablet, the second patient developed a rash and raised temperature on three occasions after taking two tablets, purpuric on one occasion, a widespread maculopapular eruption on two occasions), and two cases complained of tension (one case is described earlier above, the second case felt agitated, irritable, depressed and complained of headaches, lasting throughout eight days of treatment and stopping within 24 hours of stopping the drug). Effects on the muscular system, beneficial or otherwise, were not significant in the present series of cases, although stressed by other authors because of the relationship of meprobamate to myanesin.

Discussion

The result of this investigation did not confirm the claims made that meprobamate is a most effective drug for the treatment of tension. The selection of cases may account to some extent for the disappointing results, and the earlier less severely ill patients seen outside hospital practice may benefit more by treatment with this drug, but possibly not more than obtained using a barbiturate. West and da Fonseca (1956) report three trials, one straight trial and two "double blind" trials, comparing meprobamate with an inert tablet or amylobarbitone sodium. In the first trial the drug was most effective in the anxious group, but the results were not as favourable as those reported earlier. In the second trial there was a statistically significant superiority over the inert tablet, but in the third trial the results were comparable with amylobarbitone sodium, although some patients preferred one more than the other, suggesting that the drug differs in its action from amylobarbitone sodium and is not inactive.

The necessity of controlled trials is illustrated once again by the improvements noted with inert tablets even in patients of high intelligence.

That a few patients are benefited by the drug more than any other is suggested, but it is a question of trial and error in every case. No specific factors of sex, age or diagnostic category were elicited which could help in predicting suitable cases, other than the observation of the drug's greatest value in the symptomatic treatment of anxiety and tension in the American papers quoted.

The incidence of toxic effects has been more frequent and serious than first reported, following a pattern similar to almost every recently-introduced tranquillizing drug.

SUMMARY

Meprobamate proved less effective and less safe than previously reported in the series of 41 patients investigated. The possibility of skin eruptions and an increase in tension are two adverse reactions in particular which should be watched for. The occurrence of a rash after only one or two tablets in some cases makes this complication especially difficult to avoid.

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